at least 45bp, exclusive of the initiation codon." Figure 4 was filed as part of the '501 application. The newly added claims add no new matter to the specification.

The Rejection of Claims 60-70 Under 35 U.S.C. § 112, first paragraph

Claims 60-70 stand rejected under 35 U.S.C. § 112, first paragraph. The Advisory Action maintains that the specification does not provide a written description of the claimed invention. Applicants respectfully traverse this rejection and its supporting remarks.

The purpose of the written description requirement is to assure that the applicant was in possession of the claimed subject matter on the date the application was filed. *Vas-Cath Inc. v. Mahurkur*, 19 U.S.P.Q.2d 1111, 1116-17 (Fed. Cir. 1991). It is well known, however, that the specification need not describe subject matter of later-filed claims in *ipsis verbis* in order to satisfy the written description requirement. *In re Lukach*, 160 U.S.P.Q. 795, 796 (C.C.P.A. 1971). On the contrary, the relevant question is whether the written description in the '501 specification "convey[s] clearly to those skilled in the art, to whom it is addressed, **in any way**, the information that the applicant has invented the specific subject matter later claimed." *In re Wertheim*, 191 U.S.P.Q. 90, 97 (C.C.P.A. 1976), *appeal after remand*, 209 U.S.P.Q. 554 (C.C.P.A. 1981) (emphasis added).

The Federal Circuit has repeatedly stated that whether a specification satisfies the written description requirement, *i.e.*, conveys the information that an applicant has invented the subject matter of later filed claims, is a question of fact. *Tronzo v. Biomet Inc.*, 47 U.S.P.Q.2d 1829, 1832 (Fed. Cir. 1998); *Ex parte Daniels*, 40 U.S.P.Q.2d 1394, 1403 (Fed. Cir. 1996); *In re Alton*, 37 U.S.P.Q.2d 1578, 1580 (Fed. Cir. 1996); *Utter v. Hiraga*, 6 U.S.P.Q.2d 1709, 1714 (Fed. Cir. 1988). Moreover, because satisfaction of the written description requirement is a question of fact, "[w]hat

is needed to meet the description requirement will necessarily vary depending on the nature of the invention claimed." *In re DiLeone*, 168 U.S.P.Q. 592, 593 (C.C.P.A. 1971).

The invention claimed in this application is synthetic HIV envelope polypeptides and the use of synthetic HIV envelope polypeptides in methods of detecting HIV antibodies. The Advisory Action contends that in order to provide a sufficient written description of the invention, the specification must set forth particular synthetic peptides of the *env* gene which would be useful in immunoassays. (Advisory Action at page 3, lines 16-18). Applicants disagree with the requirement that the specification must provide a description of particular synthetic envelope peptides by reference to amino acid sequence number in order to provide an adequate written description of the claimed invention. The following facts demonstrate that the disclosure of the '501 specification does indeed provide a sufficient written description of this invention.

First, the '501 specification discloses the coding sequence of the entire *env* gene and the full-length amino acid sequence of the envelope protein. (Page 9, lines 19-21; Figure 4).

Second, the specification teaches that "polypeptides or immunologically active fragments thereof, may find use as diagnostic reagents, being used in labeled or unlabeled form . . . ." (Page 11, lines 5-7).

Third, the specification teaches how to use HIV envelope proteins and immunogenic fragments in immunoassays:

> [t]he expression products of the env and gag genes and immunogenic fragments thereof having immunogenic sites may be used for screening antisera from patients' blood to determine whether antibodies are present which bind to hTLR antigens. A wide variety of assay techniques can be employed, involving labeled or unlabeled antigens. The label may be fluorescers, radionuclides, enzymes, chemiluminescers, magnetic particles, enzyme substrates, cofactors

or inhibitors, ligands, or the like.

> A particularly convenient technique is to bind the antigen to a support and contact the blood sample with the antigen. After washing the support to remove non-specifically bound antisera, labeled antibodies to human Ig are added and specifically bound label determined.
>
> The antigenic polypeptide of hTLR may also be used as immunogens by themselves or joined to other antigens for the production of antisera or monoclonal antibodies which may be used for therapy or diagnosis. The immunoglobulins may be from any mammalian source, e.g., rodent, such as rat or mouse, primate, such as baboon, monkey or human, or the like. For diagnosis, the antibodies can be used in conventional ways to detect hTLR in a clinical sample.

(Page 14, line 17 to page 15, line 4).

Fourth, the specification teaches that "[b]ased on the nucleotide sequences, synthetic peptides may also be prepared." (Page 3, lines 15-16).

Fifth, one of skill in the art who read the '501 specification at the time it was filed would readily perceive that the disclosure relating to use of expression products of the *env* gene was equally applicable to either recombinantly produced or synthetic envelope polypeptides. (Young Declaration of March 19,1997 ¶ 9).

Sixth, **nothing** in the summary of the invention in the '501 specification in any way **limits** the application of the clear and unambiguous teaching that synthetic envelope peptides can be prepared and used in the disclosed immunoassays.

The law requires that the specification be considered as a whole when determining whether it describes a particular invention. *In re Wright*, 9 U.S.P.Q.2d 1649, 1651 (Fed. Cir. 1989). Furthermore, "[a] specification may, within the meaning of 35 U.S.C. § 112 ¶ 1, contain a written

description of a broadly claimed invention without describing all species that claim encompasses." *In re Robins*, 166 U.S.P.Q. 552, 555 (C.C.P.A. 1970). The law supports Applicants' position that the specification need not set forth particular synthetic env peptides in *ipsis verbis* in order to satisfy the written description requirement. *In re Lukach*, 442 F.2d 967, 969, 160 U.S.P.Q. 795, 796 (C.C.P.A. 1971).

Applicants' '501 specification is more than adequate to satisfy the written description requirement of 35 U.S.C. § 112, first paragraph with respect to claims 60-70. The arguments presented above apply with equal force to newly added claims 71-76. Applicants request withdrawal of the rejection of claims 60-70 under 35 U.S.C. § 112, first paragraph.

The Rejection of Claim 68 Under 35 U.S.C. § 112, first paragraph

Claim 68 stands rejected under 35 U.S.C. § 112, first paragraph. Applicants respectfully traverse this rejection and its supporting remarks.

The Office Action mailed February 17, 1998 asserted that the '501 specification "does not speak to peptides having at least 15 amino acids from the *env* region." (page 7, last line to page 8, line 4). In response, Applicants pointed out that page 9, lines 7-12 of the specification describe DNA sequences of at least 45 basepairs, which encode a polypeptide of at least 15 amino acids. (Amendment After Final Rejection filed August 17, 1998 at page 21). The Advisory Action maintains that this description in the specification does not support a synthetic peptide because the cited passage of the '501 specification allegedly describes only recombinant polypeptides. (Advisory Action at page 5, last paragraph).

The specification need not set forth synthetic peptides of at least 15 amino acids in *ipsis verbis* in order to satisfy the written description requirement. *In re Lukach*, 442 F.2d 967, 969, 160

U.S.P.Q. 795, 796 (C.C.P.A. 1971). To the contrary, as Applicants pointed out above in rebutting the rejection of claims 60-70 under 35 U.S.C. § 112, first paragraph, the specification must be considered as a whole when determining whether it describes a particular invention. *In re Wright*, 9 U.S.P.Q.2d 1649, 1651 (Fed. Cir. 1989).

The '501 specification discloses DNA sequences which encode peptides of at least 15 amino acids. (page 9, lines 3-12). The '501 specification also discloses that "[b]ased on the nucleotide sequences, synthetic peptides may also be prepared." (page 3, lines 15-16). One of skill in the art who read the '501 specification at the time it was filed would readily perceive that the disclosure relating to use of expression products of the *env* gene was equally applicable to either recombinantly produced or synthetic envelope polypeptides. (Young Declaration of March 19,1997 ¶ 9). As Dr. Young points out, "[o]ne skilled in the art would not infer from the teaching of the patent specification that production of synthetic peptides would be a teaching of a useless act." (*Id.*).

Applicants respectfully request withdrawal of this rejection of claim 68 under 35 U.S.C. § 112, first paragraph.

The Rejection of Claims 60-70 Under 35 U.S.C. § 112, first paragraph

Claims 60-70 stand rejected under 35 U.S.C. § 112, first paragraph. The Advisory Action maintains the allegation that the specification does not enable the claimed invention. Applicants respectfully traverse this rejection and its supporting remarks.

The Patent Office asserts that the specification does not enable the claimed invention because the specification itself does not identify particular synthetic peptides which would be immunoreactive with patient sera. Provided with the '501 specification, however, one of skill in the

art in 1984 would easily have been able to make synthetic peptides and to use the synthetic polypeptides in immunoassays to detect antibodies against HIV.

The Patent Office essentially requires that Applicants provide working examples of synthetic envelope polypeptides. Under controlling precedent, however, working examples are not required in order to enable the invention. *In re Long*, 151 U.S.P.Q. 640, 642 (C.C.P.A. 1966). To the contrary, whether the specification does or does not contain working examples is only one factor to be considered in determining enablement. *In re Honn,* 150 U.S.P.Q. 652, 657 (C.C.P.A. 1966). The relative skill of those in the relevant art must also be considered. *Ex parte Forman*, 230 U.S.P.Q. 546, 547 (Bd. Pat. App. Interf. 1986).

Furthermore, the law is clear that the specification need not provide knowledge which is generally known in the art. Applicants can properly rely on common knowledge in the art to bolster and supplement its disclosure. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 U.S.P.Q. 81, 94 (Fed. Cir. 1986); *Genentech Inc. v. Novo Nordisk A/S*, 42 U.S.P.Q.2d 1001, 1005 (Fed. Cir. 1997). The '501 specification, therefore, need only "supply the novel aspects of [the] invention in order to constitute adequate enablement." 42 U.S.P.Q.2d at 1005.

Applicants filed the '501 specification on October 31, 1984. Before October 31, 1984, the art possessed the following knowledge relevant to the claimed invention. First, the use of synthetic non-HIV peptides in immunoassays to detect antibodies was known and widely practiced using a variety of techniques. (Young Declaration of March 19, 1997 ¶ 8). Those techniques included, for example, ELISA assays which employed peptides immobilized on microtiter plates, test sera, and enzyme-coupled secondary antibodies. (*Id.*). Those techniques also included solid-phase radioimmunoassays that employed immobilized synthetic peptides, test sera, and ^{125}I-labeled protein

A. (*Id.*). Other methods were known in the art in 1984 for detecting specific interactions between synthetic peptides and antibodies, including radioimmunoassays that employed radioactively-labeled peptides or antibodies. (*Id.*).

Second, for proteins whose sequence was known, at least two methods of determining which peptide fragments of a protein of known sequence are immunogenic were known in the art in 1984. The skilled artisan could have identified immunogenic fragments either by routine screening or by using the Hopp algorithm. Before October 31, 1984, one skilled in the art could have constructed synthetic peptides of 15-40 amino acids. (Young Declaration of March 19, 1997 ¶¶ 13 and 15). The skilled artisan could therefore have constructed synthetic peptides and, using immunoassays well known in the art, tested serum samples for antibodies which bind to the synthetic peptides. (Young Declaration of March 19, 1997 ¶ 10). One would only need the amino acid sequence of the protein to construct the fragments and the knowledge that such fragments could be used in immunoassays. (Young Declaration of March 19, 1997 ¶¶ 9 and 10).

Alternatively, once in possession of the amino acid sequence of a protein, the skilled artisan could have used the Hopp algorithm to focus on regions of the protein which were most likely to detect antibodies against that protein. (Young Declaration of March 19, 1997 ¶ 10). The Hopp algorithm was known by those of skill in the art in 1984. (*Id.*).

At the time the '501 specification was filed, the art clearly possessed all of the knowledge and skill required to practice Applicants' invention except for the "novel aspects of [the] invention;" *i.e.*, the amino acid sequence of the envelope protein and the teaching that synthetic envelope polypeptides could be used in immunoassays to detect anti-HIV antibodies.

The '501 specification provides these novel aspects of the invention. The '501 specification

specifically teaches the 855 amino acid sequence of the HIV envelope protein (Page 9, lines 22-23, and Figure 4). Therefore, one skilled in the art could either have generated one or a panel of several envelope peptides and tested each peptide for antibody reactivity or have used the Hopp algorithm to identify antigenic envelope polypeptides and confirm this antigenicity using a prior art immunoassay. (Young Declaration of February 18, 1997 ¶¶ 5 and 7).

At the time the '501 specification was filed, panels of contiguous or overlapping synthetic peptides representing significant portions of whole polypeptides could be generated by routine methods. (Young Declaration of May 4, 1998 ¶ 8). Provided with the coding sequence and amino acid sequence of the *env* protein disclosed in the '501 specification, therefore, the skilled artisan could easily have synthesized 10- to 20-mer contiguous or overlapping synthetic *env* polypeptide fragments. *Id.* These *env* polypeptide fragments could then have been tested for antibody reactivity, using methods then known in the art. (Young Declaration of February 18, 1997 ¶ 7).

Dr. Young has also demonstrated that application of the Hopp algorithm to the sequences disclosed in the '501 specification would have identified antigenic regions of the ARV-2 envelope protein. Dr. Young used the Hopp algorithm to identify the four most hydrophilic (and therefore antigenic) regions of the ARV-2 envelope protein. (Young Declaration of March 19, 1997 ¶ 11). The most hydrophilic region of the ARV-2 envelope protein is amino acid residues 738-743 (ERDRDR). Actual later tests demonstrate that a proportion of AIDS patient antisera recognize synthetic peptides derived from these amino acid residues. (Young Declaration of March 19, 1997 ¶ 11).

The second-most hydrophilic region of the ARV-2 envelope protein is amino acid residues 653-658 (EKNEQE). (*Id.*). Actual tests demonstrate that sera from HIV-infected individuals also

recognize synthetic peptides containing these amino acids. (*Id.*).

The third-most hydrophilic region of the ARV-2 envelope protein is amino acid residues 733-738 (EEEGGE), which overlap the most hydrophilic region. (*Id.*). Actual tests demonstrate that sera from HIV-infected individuals also recognize synthetic peptides which contain these amino acids. (*Id.*).

A fourth highly hydrophilic region contains amino acid residues 505-510 (QREKRA). (*Id.*). Actual tests demonstrate that sera from HIV-infected individuals also recognize synthetic peptides which contain all or most of these amino acids. (*Id.*).

The Advisory Action asserts that one would have been "entirely unsure" whether an envelope peptide identified using the Hopp algorithm would be effective to detect specific antibodies against the envelope protein in patient sera. (Advisory Action at page 3, lines 14-15). Dr. Young's declaration and the references he cites, however, show that identification of such peptides would have been straightforward and would accurately have predicted envelope peptides which would effectively detect specific antibodies in patient sera. (Young Declaration of March 19, 1997 ¶ 11). Furthermore, the skilled artisan could have synthesized polypeptides comprising the identified antigenic regions and tested them for antibody reactivity, using methods then known in the art. (Young Declaration of May 4, 1998 ¶ 8; Young Declaration of February 18, 1997 ¶ 7).

The Patent Office has previously questioned the references which Dr. Young cited in his Declaration of March 19, 1997, to support his identification of antigenic regions of env polypeptides: "It is unclear how research publications which do not employ Hopp support Young's assertion that one of ordinary skill in the art would have applied the Hopp algorithm to select peptides for synthesis." (Office Action mailed May 28, 1997 at page 6, first full paragraph). Applicants

addressed the references cited in the Young Declaration in the only full paragraph at page 11 of the Amendment After Final Rejection filed August 17, 1998. The Advisory Action, however, questions Applicants' explanation of the relevance of the cited references. (Advisory Action at page 5, lines 1-4).

Dr. Young stated in his March 19, 1997 declaration that "one skilled in the art could have, without undue experimentation, used the sequence of ARV-2 Env provided in the '501 application to generate synthetic peptides representing most of the HIV glycoprotein. These peptides could then have been tested using standard assays known in the art, and immunogenic regions of HIV Env identified." (Young Declaration of March 19, 1997 ¶ 15). The references at issue were cited because they each support Dr. Young's demonstration that antigenic regions of env could have been identified using the Hopp protocol. Each of the cited references demonstrates that synthetic peptides containing the antigenic regions identified using the Hopp protocol were recognized by a proportion of AIDS patient antisera in actual tests. (Young Declaration of March 19, 1997 ¶ 11). That the cited references themselves did not employ the Hopp protocol is not relevant to this point.

The Patent Office must view the statements in Dr. Young's Declarations as statements of fact. *In re Alton*, 37 U.S.P.Q.2d 1578, 1583 (Fed. Cir. 1996). If the Examiner continues to dispute the facts presented in Dr. Young's Declarations, Applicants respectfully request that the Examiner provide evidence to the contrary. *Id.*

Applicants have previously cited the decision in *Chiron Corporation v. Abbott Laboratories*, 1996 U.S. Dist. LEXIS 4802 (N.D. Cal. 1996) , as directly relevant to the issue of enablement in the present application. (Amendment After Final Rejection filed August 17, 1998, paragraph bridging pages 11 and 12). In that decision, the '501 specification was judged to be enabling for the practice

of immunoassays using recombinant env antigens of any HIV strain. 1996 U.S. Dist. LEXIS 4802 * 24-25 (" . . . this court is satisfied that discovery of every possible env sequence is neither necessary nor desirable for practicing the invention. Given the '949 patent's presumption of validity and Abbott's scant showing, Chiron's representations are enough to find the patent enabling."). The Advisory Action alleges that Applicants' citation of *Chiron v. Abbott* is "improper" because the decision is unpublished. (Advisory Action at page 5, lines 4-5). That conclusion is inaccurate. The decision is **not** unpublished; it is available on Lexis and is citable as precedent. The first page of the *Chiron v. Abbott* decision, as obtained from Lexis, is included with this submission as Exhibit 3.

The '501 specification is enabling for the practice of immunoassays employing recombinant env antigens of any HIV strain. As nucleotide sequences of HIV strains would be required to make synthetic as well as recombinant envelope polypeptides, it follows logically that the '501 specification also enables the production of synthetic envelope polypeptides of any HIV strain. As the Patent Office itself points out, "it is unclear that an antibody which recognizes a particular epitope makes any such clear distinction [between a synthetic peptide and a peptide fragment generated by some other means]." (Paper No. 28 at page 3, lines 13-14). This reasoning applies with equal force to newly added claims 71-76.

Applicants respectfully request that the enablement rejection be withdrawn. If the Examiner nevertheless maintains this rejection, Applicants request under 37 C.F.R. § 1.104(d)(2) that the Examiner provide an affidavit setting forth the factual basis for the rejection.

The Rejection of Claims 60-70 Under 35 U.S.C. § 102(b) and § 102(e)

Claims 60-70 stand rejected under U.S.C. §§ 102(b) and 102(e). Applicants respectfully traverse this rejection and its supporting remarks.

To establish a *prima facie* case of obviousness based on a combination of references, the Patent Office must meet three criteria: (1) the references or the knowledge of those skilled in the art must contain a suggestion or motivation to combine the reference teachings; (2) there must be a reasonable expectation of success; and (3) the combined references must teach or suggest all the claim limitations. (M.P.E.P. § 706.02(j)). Furthermore, "[b]oth the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure." *In re Dow Chemical Co.*, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988).

The Patent Office has rejected claims 60-70 under 35 U.S.C. §§ 102(b) and 102(e) as anticipated by Chang *et al.*, U.S. Patent 4,7714,175, and Cosand, U.S. Patent 4,629,783. Applicants' invention, however, is fully described and enabled by its parent '501 specification. The subject application therefore has a priority date of October 31, 1984. Both Chang *et al.* and Cosand were filed after the '501 application. Neither reference qualifies as prior art, either to claims 60-70 or to newly added claims 71-76. Applicants respectfully request that the rejection of claims 60-70 under 35 U.S.C. §§ 102(b) and 102(e) be withdrawn.

The Rejection of Claims 60-70 Under 35 U.S.C. § 103

Claims 60-70 stand rejected under 35 U.S.C. § 103(a) as being obvious over either the combined teachings of Schupbach *et al.*, Sarngadharan *et al.*, and Popovic *et al.*, or in combination with Levy, U.S. Patent 4,716,102 and in view of the level of skill in the art as set forth in the Young

Declaration of March 19, 1997. Applicants respectfully traverse this rejection and its supporting remarks, which ignore the confusion which existed in the art in 1984.

The Patent Office has the burden of producing a factual basis for a *prima facie* case of obviousness. *In re Rijckaert*, 29 U.S.P.Q.2d 1955, 1956 (Fed. Cir. 1993). The Patent Office has attempted to build a *prima facie* case of obviousness based on either the combined teachings of Schupbach *et al.*, Sarngadharan *et al.*, and Popovic *et al.*, or in combination with Levy, U.S. Patent 4,716,102 and in view of the level of skill in the art as set forth in the Young Declaration of March 19, 1997. This attempt fails for at least three reasons. First, one of ordinary skill in the art at the time the '501 specification was filed would not have been led to combine these references. Second, even if combined, these references would not have led the ordinary artisan to Applicants' invention. Third, at the time the '501 specification was filed there was no reasonable expectation of success that a homogenous env antigen would be useful in an immunoassay.

a. One of ordinary skill in the art at the time the '501 specification was filed would not have combined the cited references.

Applicants have pointed out the confusion which existed in the art at the time the '501 application was filed in 1984. (Amendment After Final Rejection filed August 17, 1998 at pages 13-15). This confusion centered around nothing less than the **very identity** of the virus which caused AIDS. This confusion is reflected in the published scientific literature and is aptly summarized in Dr. Young's Declaration of March 19, 1997 and Affidavit of October 29, 1996 (tabs D and B in the accompanying volume of declarations) and in the April 10, 1989 Declaration of Essex and Lee (tab L in the accompanying volume of declarations).

The uncertainty over the identity of the AIDS virus is clearly evidenced by the fact that two

of the most active and well-respected AIDS research laboratories in the world, the laboratories of Luc Montagnier and Robert C. Gallo, did not agree even on the family to which the "AIDS virus" belonged, much less agree on its actual identity. Montagnier's group postulated that the virus was related to equine infectious anemia virus (EIAV). (Montagnier *et al.*, *Science 225*, 63-66, 1984). Gallo's group, on the other hand, announced that the virus was "a true member of the HTLV family." (Schupbach *et al.*, *Science 224*, 503-505, 1984; Young Affidavit of October 26, 1996 ¶¶ 12 and 13; Young Declaration of March 19, 1997 ¶ 19). Gallo's group also announced that there was extensive antibody cross-reactivity and sequence homology between HTLV-III and HTLV-I and II. (*Id.*; Arya *et al.*, *Science 225*, 927-30, 1984; Sarngadharan *et al.*, *Science 224*, 506-08, 1984; Young Affidavit of October 26, 1996 ¶ 12). This identification was later found to be erroneous. (Gallo, VIRUS HUNTING: AIDS, CANCER, AND THE HUMAN RETROVIRUS: A STORY OF SCIENTIFIC DISCOVERY, New Republic Books, 1991, at pages 143 and 152; Young Declaration ¶ 19; Young Affidavit of October 29, 1996 ¶ 12).

Identification of the AIDS virus was an important issue in 1984, and one of ordinary skill in the art would certainly have read these two publications from eminent scientists in the field. It is equally clear that one of ordinary skill in the art, reading these two publications, would not have been confident that the identity of the virus which caused AIDS had been established.

Popovic *et al.* provides further evidence of the confusion and uncertainty surrounding identification of the AIDS virus:

> The transient expression of cytopathic variants of HTLV in cells from AIDS patients and the previous lack of a cell system that could maintain growth and still be susceptible to and permissive for the virus represented a major obstacle in detection, isolation, and elucidation of the precise causative agent of AIDS.

(Popovic *et al.*, *Science 224*, 497, 500, 1984). The difficulty of growing the AIDS-causing virus *in vitro* was well known in 1984. (Young Declaration of March 19, 1997 ¶ 17).

The art cited by the Patent Office reflects this confusion. For example, there is no indication in Schupbach *et al.* that envelope proteins had been identified by antibodies in the sera of the AIDS patients which were tested. The authors of Schupbach *et al.* themselves characterized their report as a "**preliminary** biochemical and immunological analysis." (*Science 224* at 503, emphasis added). The report provides **no** amino acid sequence data. (Young Declaration of March 19, 1997 ¶ 17). The only mention of envelope proteins in the entire article is at page 505, at the top of column 2, which states:

> The detection of p65 by many of the serum samples is of special interest. We have tested these sera on strips prepared from lysates of cells producing HTLV-I or -II. Some of the cells produce a p65 that has been shown (*13*) to be coded for by the *env* gene of HTLV-I and to be the homolog of the gp61 described by others (*11, 12*). Many of the sera recognizing p65 in HTLV-III-infected cells also recognized, **though somewhat faintly**, p65 in cells producing HTLV-I or -II, and some of them also recognized *gag*-related antigens (data not shown).

(*Id.* at 505, emphasis added). Reference 13, which is cited as teaching that the *env* gene of HTLV-I encodes a 65 kD protein, is a manuscript of Schupbach, Sarngadharan, and Gallo. (*See* reference list of Schupbach *et al.* at page 505). At the time Schupbach *et al.* was published, reference 13 was **in press** and therefore not available to those of skill in the art. It is axiomatic that those of ordinary skill in the art do not accept conclusions of a scientific report until the data which underlies those conclusions has been examined and, preferably, replicated. Moreover, the cited passage goes on to point out that the recognition of p65 by sera of AIDS patients was "faint." A faint immune response would not lead one of ordinary skill in the art to the conclusion that the p65 protein, whatever its

identity, would be a good candidate for use in diagnostic immunoassays.

In fact, even the authors of Schupbach *et al.* do not assert that they had truly identified **viral** protein antigens. Schupbach *et al.* characterized the immunoreactive proteins they detected as "**either** virus-coded proteins **or** cellular antigens specifically induced by the infection." (*Id.* at page 505, emphasis added). Schupbach *et al.* not only does not teach the amino acid sequence of an envelope protein, it also does not even unambiguously identify a viral envelope protein of an AID-associated virus. Nor do any of the references suggest using a synthetic envelope polypeptide in an immunoassay.

Sarngadharan *et al.* separated protein components from purified HTLV-III using SDS-polyacrylamide electrophoresis; among these protein components was "a protein with a molecular weight of 41,000 (**presumably** the envelope glycoprotein) . . . ." (*Science 224*, 506, 507, May 4, 1984), emphasis added. Again, at page 508, Sarngadharan *et al.* refers to the 41 kD immunoreactive protein as being "**presumably** the envelope protein." As in Schupbach *et al.*, no amino acid sequence data is provided. Furthermore, the immunoreactive protein identified in Sarngadharan *et al.* has a molecular weight of 41 kD, compared with the 65 kD protein identified in Schupbach *et al.* It would certainly not be clear to the artisan of ordinary skill how a 41 kD and a 65 kD protein could both be the envelope protein of the AIDS virus. One would at least be led to reserve judgment about which, if indeed either, of the reported 41 or 65 kD proteins might be the viral envelope protein of the AIDS associated virus.

Similarly, Popovic *et al.* barely mention envelope proteins in their 1984 report:

> Also consistent with an HTLV etiology were the results of Essex and Lee and their colleagues showing the presence of antibodies to cell membrane antigens of HTLV-infected cells in serum samples from

> more than 40 percent of patients with AIDS (*23*). This antigen has since been defined as part of the envelope of HTLV (*24*).

(*Science 224*, 497, 497, May 4, 1984). Popovic *et al.* does not even provide a molecular weight for the alleged envelope protein antigen.

Sarngadharan *et al.*, Schupbach *et al.*, and Popovic *et al.* cite references which do not disclose amino acid sequence data and which disagree even on a possible molecular weight for an envelope protein antigen. These meager combined teachings in Sarngadharan *et al.*, Schupbach *et al.*, and Popovic *et al.* regarding envelope protein antigens could not lead one of ordinary skill in the art to Applicants' invention, which requires knowledge of the amino acid sequence of the AIDS virus envelope protein as well as the suggestion to use a synthetic envelope polypeptide in an immunoassay.

To obtain the amino acid sequence of the envelope protein for use in practicing the invention, one must either clone the virus and obtain the coding sequence of the protein or obtain enough envelope protein for amino acid sequencing. In either case, propagation of sufficient amounts of the virus in cell lines *in vitro* is required. Primary human cells, however, fail to produce significant quantities of HIV, as the virus is cytopathic and rapidly killed the infected virus-producing cells. (Young Declaration of March 19, 1997 ¶ 17). Therefore, a person of ordinary skill in the art who attempted to generate sufficient quantities of envelope protein for sequencing would have (1) had to obtain an appropriate established cell line known to produce the virus and (2) had to have a knowledge of the precise conditions required for infecting those cells and for maintaining the infected cells for long periods of time in culture. (Young Declaration of March 19, 1997 ¶ 17).

Teachings in the cited references regarding the cell line which could be used to propagate the

HTLV-III virus, however, are not sufficient to enable one of ordinary skill in the art to obtain sufficient quantities of HTLV-III. Sarngadharan *et al.*, Schupbach *et al.*, and Popovic *et al.* all originated from Gallo's laboratory and all employed the same cell line. Sarngadharan *et al.* discloses only that "virus was purified from supernatants of cell cultures supporting the continuous production of HTLV-III" and refers to Popovic *et al.* (*Science 224* at 507). Schupbach *et al.* states only that "two immortalized and infected human T-cell clones, H4/HTLV-III and H17/HTLV-III" were used and also refers to Popovic *et al.* (*Science 224* at 503).

Popovic *et al.* states only that the cell line is a "neoplastic aneuploid T-cell line, derived from an adult with lymphoid leukemia . . . ." (*Science 224* at 498). The cell line itself is not described in detail. No culture conditions, beyond the use of RPMI 1640 medium containing fetal calf serum, antibiotics, and T-cell growth factor (IL-2) are provided. Given the well-known difficulty of maintaining AIDS virus-infected cells *in vitro*, one of skill in the art would not have had a reasonable expectation that establishing a neoplastic aneuploid T-cell line from an adult with lymphoid leukemia, without guidance as to the characteristics of the cell line or even how to maintain it in culture, would be successful. (Young Declaration of March 19, 1997 ¶ 17). In fact, a more reasonable conclusion from reading Popovic *et al.*, together with a background knowledge of the state of the art, would have been that the cells from this particular patient were unique and that there were manipulations, not revealed in Popovic *et al.*, which permitted growth of retrovirus-infected cells *in vitro*. As the report identifies the patient only by initials, there would have been no reasonable or ethical way for an ordinary artisan to have obtained another sample of these cells and to have established another useful cell line.

Furthermore, it was not certain in 1984 that Sarngadharan *et al.*, Schupbach *et al.*, and

Popovic *et al.* were indeed working with **the** AIDS virus. In 1984, at the time Schupbach *et al.*, Sarngadharan *et al.*, and Popovic *et al.* were published, the state of the art did not permit the conclusion that HTLV-III was the causative agent of AIDS. This confusion is reflected in the published scientific literature and is aptly summarized in Dr. Young's Declaration of March 19, 1997 and Affidavit of October 29, 1996 (*see* the volume of declarations at tabs D and B, respectively) and in the April 10, 1989 Declaration of Essex and Lee (at tab L in the volume of declarations). Therefore, even if *arguendo* the references disclosed amino acid sequences and/or sufficient information to reproduce the cell line so that sufficient quantities of HTLV-III proteins could be produced, these references would not have made Applicants' invention obvious.

b. Even if *arguendo* one of ordinary skill in the art would have combined the cited references, these references would not have led the ordinary artisan to Applicants' invention.

Applicants' invention requires knowledge of the amino acid sequence of the AIDS virus envelope protein, because Applicants' claims recite use of a **synthetic** polypeptide. The invention also requires the suggestion or teaching to use the synthetic polypeptides in an immunoassay. One cannot synthesize a polypeptide without knowing its amino acid sequence. The Patent Office cannot meet its burden of establishing a *prima facie* case that Applicants' invention, including the amino acid sequence of the envelope protein, would have been obvious because (1) none of the cited references teach an amino acid sequence of an immunogenic envelope protein of an unambiguously identified AIDS virus and (2) none of the cited references disclose means by which an envelope protein could be obtained in sufficient quantity to determine its amino acid sequence. Combination of these references, therefore, could not have led one of ordinary skill in the art to Applicants' invention.

Even if, *arguendo*, one were to assume that in 1984 the identification of the AIDS virus had been established conclusively, the combined teachings of Schupbach *et al.*, Sarngadharan *et al.*, and Popovic *et al.* could not have led an ordinary artisan to Applicants' claimed invention. None of these references conclusively identifies **any** protein as an envelope protein. None of these references provides amino acid sequences. None of these references provides details for obtaining or propagating the cell line used in order to obtain quantities of the viral proteins or genes for sequencing. Nor do any of the references suggest using a synthetic polypeptide in an immunoassay. Thus, Applicants' invention, which requires both knowledge of the amino acid sequence of the envelope protein of the causative agent of AIDS and the teaching that synthetic env polypeptides can be used in an immunoassay, would not have been obvious in view of the combined teachings of Schupbach *et al.*, Sarngadharan *et al.*, and Popovic *et al.* The combined teachings of the cited references therefore do not establish a *prima facie* case of obviousness.

Neither Levy U.S. Patent 4,716,102 nor the level of skill in the art described in the Young Declaration of March 19, 1997 cure the deficiencies of the combined teachings of Schupbach *et al.*, Sarngadharan *et al.*, and Popovic *et al.* Levy discloses an AIDS-associated retrovirus, ARV-2, and a human T cell line infected with ARV-2. Nowhere does Levy provide amino acid sequences or teach or suggest that ARV-2 is the HTLV-III virus of Schupbach *et al.*, Sarngadharan *et al.*, and Popovic *et al.* In fact, Levy teaches that ARV-2 is distinct from LAV and, therefore, from HTLV-III. (Levy, column 1, lines 43-45 and 54-55). As the '501 specification points out, this relationship could only be determined by sequencing the genomes of the two viruses and demonstrating that they are identical. (Page 1, lines 26-32).

The Patent Office uses impermissible hindsight to select the cited references.

> To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed.

(*In re Rouffet*, Fed. Cir. No. 97-1492, July 15, 1998). In this case, the Patent Office has not satisfied the requirement to demonstrate a motivation to combine the cited references.

Nor can the state of the art, as described in the Young Declaration of March 19, 1997, fill in the gap which is missing from Schupbach *et al.*, Sarngadharan *et al.*, Popovic *et al.*, and Levy. Applicants' invention requires knowledge of the amino acid sequence of the AIDS virus envelope protein and the suggestion to use a synthetic envelope polypeptides in an immunoassay. None of the cited references provides the amino acid sequence of an HIV envelope protein or sufficient disclosure of a starting material which would provide one of ordinary skill in the art with a reasonable expectation of success of identifying immunogenic envelope polypeptides of a virus which causes AIDS. It is Applicants who first disclosed the complete sequence of an HIV isolate and the first accurate identification of the *env* gene and its reading frame. It is Applicants' description of the *env* gene and reading frame which permits synthetic production of env polypeptides with defined amino acid sequences for diagnostic and therapeutic purposes. It is also Applicants' contribution to the art to teach that synthetic env polypeptides can be used in immunoassays.

The Advisory Action states that in traversal of the rejection under § 103, Applicants have argued that the state of the art was different than that described in Dr. Young's declaration.

(Advisory Action at page 5, lines 8-11). Applicants have made no such argument. In characterizing the state of the art in 1984, Applicants have argued that (1) the identity of the AIDS virus was in serious question, (2) identity of the envelope protein was not established, and (3) the information required to reproduce Popovic's cell line was unavailable to the art. Dr. Young has sworn to points (1) to (3) in ¶¶ 17-19 of his March 19, 1997 declaration.

The Advisory Action also alleges that Applicants have argued that even with Levy's virus, "no amount of skill" would have led one to Applicants' invention. This allegation mischaracterizes Applicants' argument. Applicants have pointed out that the relationship between Levy's virus and the HTLV-III virus of Schupbach *et al.*, Sarngadharan *et al.*, and Popovic *et al.* was unclear. (Amendment After Final Rejection at page 19, first full paragraph). Applicants have also pointed out that it is they who provided this link, by sequencing Levy's ARV-2 virus and providing the art with that sequence. (*Id.* at page 20, first paragraph). Use of synthetic HIV envelope polypeptides in an immunoassay cannot be obvious if the starting material necessary to obtain amino acid or DNA sequences from which to construct the synthetic polypeptides is not sufficiently described or taught.

Again, the Patent Office has used impermissible hindsight to select the cited references. Although it is now known that the virus studied in the cited references is the same virus whose sequence is taught in Applicants' specification, it is improper to conclude that therefore Applicants' invention would have been obvious at the time the '501 specification was filed.

c. At the time the '501 specification was filed there was no reasonable expectation of success that a homogenous env antigen would be useful in an immunoassay.

The references cited by the Patent Office do not demonstrate that, in the absence of the '501 specification, one of ordinary skill in the art would have had a reasonable expectation of success that a homogeneous env antigen would be useful in an immunoassay. Because of the mutable nature of HIV viruses, the cell cultures infected with HIV virus, such as the cells used in the cited references, will comprise *env* sequences which vary. (Declaration of Dr. Kathelyn Steimer, at tab I of the submitted volume of declarations, ¶ 9). HIV is a retrovirus that replicates via RNA-dependent reverse transcriptase encoded in the *pol* domain of HIV. (Steimer Declaration ¶ 9). It is well known that reverse transcriptases do not make authentic copies during the replication cycle of the virus, and the misincorporation rate of HIV reverse transcriptase has been estimated to be about 10^{-4} per base, which is equivalent to one nucleotide change per genome per replication cycle. (Meyerhans *et al.*, *Cell 58*, 901-10, 1989, at page 901, column 1; Steimer Declaration ¶ 9). It has therefore been statistically shown that no two HIV proviruses (the DNA replicate of the viral genome made *in vivo*) are identical. (Wain-Hobston, *AIDS 3 (Suppl. 1)* S13-18, 1989, at S13, column 1; Steimer Declaration ¶ 9). Thus, a "single" viral isolate is actually heterogeneous and consists of many variants. (Fenyo *et al.*, *AIDS 3 (Suppl. 1)* S5-12, 1989, at S6, column 1; Steimer Declaration ¶ 9).

The references cited above show specific examples of the heterogeneous nature of HIV. (Steimer Declaration ¶ 10). For example, Figure 5 of Meyerhans *et al.* compares the amino acid sequence of a very small protein, tat, encoded by the HIV genome. (Steimer Declaration ¶ 10). Three different groupings of heterogeneous amino acid sequences found in samples taken from cell culture are shown as groupings L1-L3. (Steimer Declaration ¶ 10). They are compared to a

heterogeneous grouping of tat amino acid sequences found in samples of viral isolates taken directly from a patient (V1-V3). (Steimer Declaration ¶ 10). As can be seen, sample L1 had at least seven different "species" of tat protein; sample L2 contained at least eight different proteins; and sample L3 was a heterogeneous mixture also of at least eight different proteins. (Steimer Declaration ¶ 10). Wain-Hobson reiterates this same data in Figure 2, with the addition of similar data for the env domain shown in Figure 1 at page S14. (Steimer Declaration ¶ 10). Wain-Hobson also observed sequence changes in the gag domain. (Wain-Hobson at S15, column 1; Steimer Declaration ¶ 10).

The sequence heterogeneity or polymorphism has been observed with the HIV isolates which were known in 1984. (Steimer Declaration ¶ 11). For example, Wain-Hobson noted polymorphism for both the LAV-1 and HTLV-III_B isolates, as well as in the clones specifically disclosed in papers and patent applications of researchers at the Institut Pasteur and National Institutes of Health.

Based upon the foregoing, it is clear that a polypeptide composition comprised of any particular antigen isolated from native virus, grown in culture or otherwise, will necessarily constitute a mixture of similar, but not identical, proteins which are heterogenous in amino acid sequence. (Steimer Declaration ¶ 12). It is axiomatic that a synthetic polypeptide, on the other hand, is inherently homogeneous relative to the lysate-derived HIV antigens, because only one amino acid sequence is synthesized.

Early HIV immunoassays used lysates, which were though to be necessary due to the heterogeneity of the virus. (Steimer Declaration ¶ 12). Because no two HIV isolates were identical, it may have been important in screening blood samples from a diversity of human subjects to have some variation in antigen sequences to improve the chances of binding as many anti-HIV antibodies as possible. (Steimer Declaration ¶ 12). Dr. Weiss has stated that, as of October 1984, an ordinarily

skilled scientist working in the field would not have had a reasonable expectation that a **recombinant**-based HIV envelope screening/diagnostic immunoassay would be as effective as an immunoassay based on the native virus. (Weiss Report at page 9, lines 1-4). Dr. Steimer has also stated that it would not have been obvious that an immunoassay employing recombinant polypeptides would work in view of the known heterogeneity of the HIV virus. (Steimer Declaration ¶ 13). The basis for this conclusion is that a recombinant env polypeptide would be homogenous. (*see* Steimer Declaration ¶ 13). Therefore, the ordinary artisan would also not have had a reasonable expectation of success that synthetic env polypeptides would be useful in an immunoassay to detect antibodies against HIV, because synthetic polypeptides are also homogeneous.

That Applicants' immunoassays **do** work, however, is evidenced by the FDA's Summary Basis of Approval of a commercial assay which embodies Applicants' invention, "Human Immunodeficiency Virus Types 1 and 2 (Synthetic Peptide)" (attached as Exhibit 4). In order for this assay to have been approved by the FDA, it must have been proven safe **and effective** in clinical trials. In fact, the assay must have satisfied two "effectiveness" criteria, sensitivity and specificity. (Weiss Report at page 8, lines 16-26).

To establish a *prima facie* case of obvious, "[b]oth the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure." *In re Dow Chemical Co.*, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). None of the cited references teach or suggest that synthetic env polypeptides can be used in an immunoassay to detect antibodies against HIV. This teaching is found only in the '501 specification. In view of the heterogeneity of the HIV virus, without the teachings of the '501 specification, one of ordinary skill would have had no reasonable expectation of success that a homogeneous env antigen would be useful in an immunoassay.

As demonstrated above, the Patent Office has failed to carry its burden of establishing a *prima facie* case of obviousness. This reasoning applies with equal force to newly added claims 71-76. Applicants therefore respectfully request withdrawal of the rejection under 35 U.S.C. § 103(a).

Conclusion

The Patent Office has failed to show that Applicants claims 60-70 are not fully supported and enabled by the '501 specification. The Patent Office has also failed to establish a *prima facie* case that claims 60-70 are obvious. These arguments apply with equal force to newly added claims 71-76. Applicants therefore request a speedy allowance of claims 60-76.

Please continue to address all further correspondence in this application to Alisa A. Harbin, Registration No. 33,895, Chiron Corporation, Intellectual Property Dept., R440, 4560 Horton Street, Emeryville, CA 94608-2916.

Respectfully submitted,

Dated: March 5, 1999 By: Lisa M. Hemmendinger

Lisa M. Hemmendinger
Registration No. 42,653

Banner & Witcoff, Ltd.
1001 G Street, N.W.
Suite 1100
Washington, D.C. 20001-4597
(202) 508-9100
DHH/LMH